ACTA MYOL 2026;XLV:77-81;
DOI: 10.36185/2532-1900-2740

CASE REPORT

A case of childhood-onset oculopharyngeal myopathy with a novel HNRNPA2B1 duplication

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Objectives. To describe the clinical, histological, genetic, and long-term clinical features of an early-onset oculopharyngeal muscular dystrophy (OPMD)-like myopathy associated with a novel HNRNPA2B1 variant, and to highlight the importance of re-evaluating unresolved myopathies.
Methods. We report a 41-year-old Italian woman with childhood-onset ptosis, ophthalmoparesis, proximal and axial weakness, and dysphagia. Clinical, radiological, histological, and genetic data collected over more than two decades were reviewed. Muscle biopsies underwent routine histochemical, immunohistochemical, and ultrastructural assessment. Previous testing included PABPN1 GCN repeat expansion analysis and mitochondrial DNA analyses - including mtDNA rearrangements and mtDNA NGS sequencing. Extended next-generation sequencing using a myopathy panel was subsequently performed, followed by parental segregation analysis.
Results. Symptoms began at age 6 with bilateral ptosis and progressed slowly to severe ophthalmoparesis, facial, axial, and proximal limb weakness, dysphagia, and respiratory impairment. Muscle biopsies showed rimmed and autophagic vacuoles, centralized nuclei, and minor mitochondrial changes. Long-term follow-up documented ineffective cough, mild restrictive respiratory involvement with recurrent pneumonias, early-onset osteoporosis with multiple fractures, and severe jaw contracture, without cardiac or central nervous system involvement. Extended genetic testing identified a novel heterozygous likely pathogenic HNRNPA2B1 duplication, c.1036_1037dup, p.(Tyr347ValfsTer25), not detected in the segregation analysis in both parents.
Conclusions. This case expands the phenotypic spectrum of rare HNRNPA2B1-related early-onset OPMD-like myopathy and provides longitudinal evidence and degree of multisystem involvement. Periodic diagnostic re-evaluation of unsolved myopathies in the genomic era may improve diagnosis, multidisciplinary management, and genetic counselling.

Key words: oculopharyngeal muscular dystrophy (OPMD), HNRNPA2B1, Ophthalmoparesis, rimmed vacuoles, childhood-onset

Received: August 14, 2026
Accepted: September 28, 2026

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How to cite this article: Urbano G, Gadaleta G, Leopizzi E, et al. A case of childhood-onset oculopharyngeal myopathy with a novel HNRNPA2B1 duplication. Acta Myol 2026;45:77-81. https://doi.org/10.36185/2532-1900-2740

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Introduction

Oculopharyngeal muscular dystrophy (OPMD) is a rare neuromuscular condition characterized by progressive ptosis, ophthalmoparesis, dysphagia, and proximal myopathy. OPMD usually presents in adulthood, with a median age of onset around 50 years; childhood-onset cases are extremely rare. This condition results from heterozygous or biallelic pathogenic expansion of the first exon of PABPN1, conferring either a possible autosomal dominant or recessive condition [1]. RNA-binding proteins (RBPs) regulate gene expression and cellular function. Pathogenic variants in RBP genes are associated with multisystem proteinopathies (MSPs), including motor neuron disease, frontotemporal dementia (FTD), inclusion body myopathy, and Paget's disease of the bone [2,3]. A case series of 11 patients

from 10 unrelated families described early-onset OPMD associated with heterozygous HNRNPA2B1 frameshift in the C-terminal region [4,5]. In this case, we report a novel HNRNPA2B1 duplication in the already reported domains associated with an OPMD-like phenotype and longitudinal multisystem involvement.

Materials and methods

The study involved an Italian woman affected by a childhood-onset myopathy. After obtaining informed consent, a right quadriceps muscle biopsy was performed at our center in 1996. Histochemical staining included haematoxylin and eosin (H&E), cytochrome c oxidase (COX), combined COX-succinate dehydrogenase (COX-SDH), nicotinamide adenine dinucleotide (NADH), modified Gomori trichrome, lactate dehydrogenase (LDH), succinate dehydrogenase (SDH), periodic acid-Schiff (PAS), and Sudan staining. Electron microscopy was performed. A left quadriceps biopsy was subsequently performed at another center (2002), where histochemical and immunohistochemical staining analyses were performed.

Genetic analysis for PABPN1 GCN repeat expansion in peripheral blood (2002) as well as the assessment of mitochondrial DNA rearrangements on muscle tissue by Southern Blot had been previously performed. Complete mtDNA NGS analysis was performed on a blood sample in 2018. Peripheral blood was collected from the patient and her parents after written informed consent was obtained, and an NGS panel for myopathies, including 213 genes, was performed in 2024. Genomic DNA was extracted from the blood through the QIAsymphony extraction system (QIAGEN). The mean sequencing depth was 172x. At the variant site, 84 alternate and 88 reference reads were observed. The findings in the proband and her parents were confirmed by Sanger sequencing. The study was authorized by the Medical Direction of the AOU Città della Salute e della Scienza di Torino - prot. N° 0019574.

Results

The 41-year-old female patient first accessed our outpatient clinic at age 12 (1996) for myalgias and bilateral ptosis since age 6, with a slowly progressive course. No neurodevelopmental abnormalities were detected. Family history was negative for neuromuscular disease; her asymptomatic parents were not consanguineous but originated from the same geographical area.

On initial clinical examination, the patient showed axial and proximal weakness and hypotrophy, short stature, bilateral ptosis, and ophthalmoparesis without diplopia and multiple limb contractures. Serum CK was mildly elevated (250-860 U/L, up to x4 ULN), while serum lactate was within the normal range; electromyography showed myopathic changes in proximal muscles and the orbicularis oculi.

The patient underwent a right quadriceps muscle biopsy (age 12), which revealed several fibers presenting rimmed vacuoles, moderate size variability, and centralized nuclei; no major COX/SDH alterations were detected (Fig. 1). NADH staining showed moth-eaten fibers, while electron microscopy demonstrated autophagic vacuoles and mitochondrial accumulation.

In the following years, the patient developed swallowing difficulties, for which she was evaluated at another neuromuscular center, and

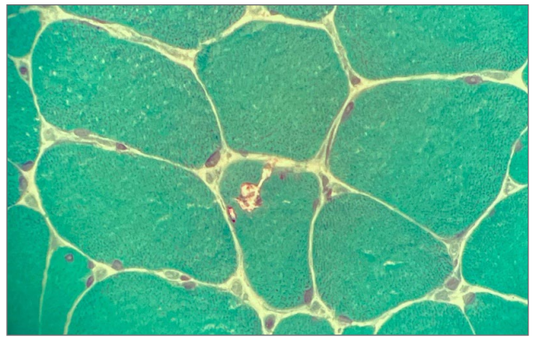


Figure 1. A section of the patient's right quadriceps muscle biopsy showing size variability and a rimmed vacuolated fiber in modified Gomori Trichrome Staining - x 25.

a second muscle biopsy was prompted (age 18). The left quadriceps sample examination confirmed the previous findings, also highlighting the presence of a few 'ragged red-like' fibers compatible with mitochondrial alterations, as well as minor neurogenic changes. No COX/SDH alterations were documented.

Given the clinical presentation and the histological findings, genetic analyses for PABPN1 expansion and mtDNA rearrangements were requested and tested negative. In light of the clinical presentation and the state of genetic knowledge available at the time, the overall findings were considered consistent with a mitochondrial myopathy, despite the atypical histological presence of rimmed vacuoles. Supplementation with ubidecarenone, carnitine, and riboflavin was started, with partial benefit on fatigue and muscle strength.

Ophthalmologically, the patient experienced slow progression of the ophthalmoparesis and recurrent ptosis, despite two blepharoplasties (2005-2019). Dietary adaptation and behavioral strategies prevented major dysphagic events and resulted in stable weight maintenance. Because of an ineffective cough, the patient was started on cough assistance at age 33. Mild reductions in FVC and FEV1 were detected, but the patient did not require mechanical ventilation; however, in recent years, the patient experienced two episodes of pneumonia requiring hospital admissions for intravenous antibiotic treatment (2018-2022). Serial Holter ECG and echocardiography did not document cardiac involvement, and multiple brain MRIs (last in 2025) showed no pathological changes.

Serum CK levels remained mildly elevated (2x-4x ULN); apart from low vitamin D, no bone health abnormalities were detected, but from age 31 onward, the patient experienced a lumbar L2 fracture and three post-traumatic fractures of the lower limbs (left femur, left tibia and fibula). Initially, densitometric values compatible with osteopenia (age 32) and then osteoporosis (age 37) were observed, and intravenous bisphosphonate therapy was initiated at age 37 (Fig. 2). The patient also developed a severe jaw contracture that required two surgical procedures (age 23 and 39) with only partial benefit.

After a recent review of the clinical data, the patient consented to an extension of the genetic testing: mtDNA NGS sequencing (2018) tested negative, while an NGS panel of nuclear genes associated

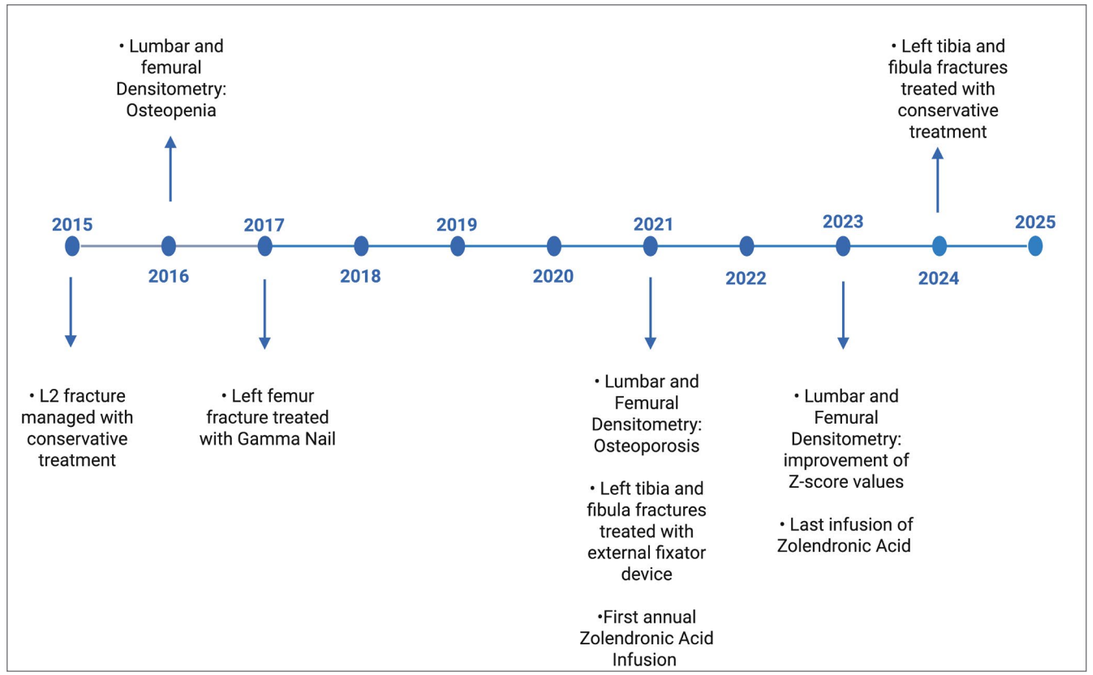


Figure 2. Longitudinal bone health findings during follow-up. *Created in BioRender. Urbano, G.* (2026). https://BioRender.com/wq9wkzz

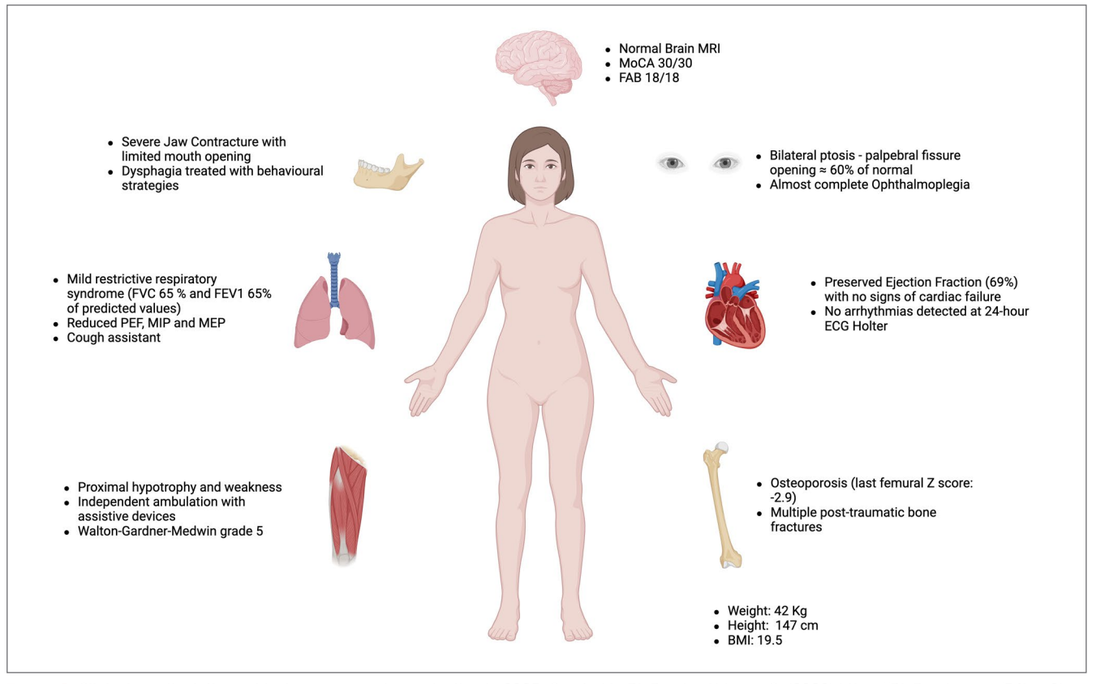


Figure 3. Clinical manifestations at last neuromuscular evaluation in 2025. Created in BioRender. Urbano, G. (2026) https://BioRender.com/54hap3j.

with myopathies - including congenital myasthenic syndromes (CMS) and nuclear genes related to primary mitochondrial disorders (PMD) - identified the heterozygous frameshift variant c.1036_1037dup, p. (Tyr347Valfs Ter25) in HNRNPA2B1 (NM_031243.3, hg38 chr7:26192540, exon 10). The segregation analysis did not detect the variant in either parent, supporting a presumed de novo occurrence, although the biological parentage was not independently confirmed. According to the ACMG criteria, the variant here found was classified as likely pathogenic (PM2_Supporting, as it is not indexed in gnomAD v4.1, PVS1_Strong; PM6_Moderate).

At the most recent neurological evaluation (2025), the patient had bilateral ptosis with almost complete ophthalmoplegia, mild facial weakness, proximal weakness and hypotrophy, more pronounced in the lower limbs, and a rhinolalic voice. Cognitive functions were intact (Montreal Cognitive Assessment 30/30 and Frontal Assessment Battery 18/18). Postural changes and ambulation were independent with assistive devices; a manual wheelchair was provided for longer trips. A moderate-to-moderately severe level of disability was assessed through a grade 5 on the Walton-Gardner-Medwin scale.

The phenotype at last evaluation is summarized in Figure 3.

Discussion

Childhood-onset myopathies with ocular involvement have a broad differential diagnosis, mainly including primary mitochondrial myopathies, metabolic myopathies, congenital myopathies, congenital myasthenic syndromes, myotonic dystrophy, and CNS disorders. Clinical, histological, and laboratory findings raised suspicion of oculopharyngeal muscular dystrophy, prompting PABPN1 GCN repeat testing and analysis of mtDNA rearrangements despite the atypical age at onset.

The subsequent more comprehensive genetic testing allowed the identification of a clinically consistent likely pathogenic presumed de novo variant in HNRNPA2B1. This novel variant is predicted to result in the same protein alteration reported in one of the cases (F10, P11) presented by Kim et al. [4]. It is located in the highly conserved LCD, whose alterations may result in the formation of intracellular protein aggregates. HNRNPA2B1 is one of the pleiotropic genes responsible for multisystem proteinopathies (MSPs), a heterogeneous set of conditions caused by defects in RNA-binding proteins (RBP) and clinically characterized by protein aggregates in different tissues, including brain, muscle, and bone [4]. In the case series by Kim et al, the heterozygous frameshift variants associated with early-onset OPMD were shown to increase the cytoplasmic protein concentration and reduce nuclear import, in contrast to the pathogenic process underlying other MSPs [4]. Although it has not yet been fully established, the evidence currently available suggests that frameshift variants in these LCDs of HNRNPA2B1 may promote the formation of cytoplasmic dysfunctional protein aggregates.

Our case provides detailed longitudinal characterization despite the lack of functional data. Consistent with previous reports, our patient showed childhood-onset slowly progressive axial and proximal myopathy with recurrent ptosis and severe ophthalmoparesis. Swallowing difficulties progressed gradually, while oral nutrition remained preserved despite recurrent jaw contractures. Respiratory involvement was characterized by a reduced cough peak, reduced MIP and MEP, recurrent infections, and a mild restrictive respiratory syndrome (FVC 65% predicted, FEV1 65% predicted) without the need for mechanical ventilation.

Notably, our patient presented multiple post-traumatic fractures with early-onset osteoporosis requiring bisphosphonate treatment with only partial benefit. The observation of low bone density with a negative Paget's bone screening and the concurrence of multiple factors - including reduced mobility and muscle weakness - support attention and monitoring in these patients.

Conclusions

This case underscores the value of a comprehensive phenotyping in the complex differential diagnoses of early-onset myopathies with ocular involvement. The longitudinal follow-up in a patient with a novel HNRNPA2B1 duplication affecting the LCD contributes to enriching the phenotypic spectrum of these rare cases of early-onset OPMD-like myopathy. Finally, revising unsolved cases in the current 'genomic era' is fundamental to providing the appropriate multidisciplinary care and proper genetic counselling.

List of Abbreviations

ACMG (American College of Medical Genetics and Genomics); CMS (Congenital Myasthenic Syndrome); CK (Creatine Kinase); COX (Cytochrome c Oxidase); COX-SDH (Cytochrome c Oxidase-Succinate Dehydrogenase); ECG (Electrocardiogram); FEV1 (Forced Expiratory Volume in One Second); FTD (Frontotemporal Dementia); FVC (Forced Vital Capacity); HNRNPA2B1 (Heterogeneous Nuclear Ribonucleoprotein A2/B1); LCD (low-complexity domain); LDH (Lactate Dehydrogenase); MEP (Maximal Expiratory Pressure); MIP (Maximal Inspiratory Pressure); MRI (Magnetic Resonance Imaging); MSP (Multisystem Proteinopathy); mtDNA (Mitochondrial DNA); NADH (Nicotinamide Adenine Dinucleotide, Reduced Form); NGS (Next-Generation Sequencing); OPMD (Oculopharyngeal Muscular Dystrophy); PABPN1 (Polyadenylate-binding Nuclear Protein 1); PAS (Periodic Acid-Schiff); PMD (Primary Mitochondrial Disorders); RBP (RNA-Binding Protein); SDH (Succinate Dehydrogenase); ULN (Upper Limit of Normal).

Acknowledgements

We are grateful to the patient and her family in our research study.

Funding

No external funding was provided.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

U.G., G.G., and V.L. contributed to patient evaluation. U.G. and L.E. prepared the manuscript. P.G. performed and evaluated the genetic tests. L.E. contributed to the preparation and staining of the muscle biopsy. V.L., and U.G. analyzed and interpreted the muscle biopsy. V.L. supervised and finalized the manuscript.

Ethical consideration

The study was conducted according to the 1964 Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Data availability

The data presented in this study are available on request. The data are not publicly available due to privacy restrictions.

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